

**Amendment and Response**

Derek David SMITH et al.

Serial No.: 09/813,345

Confirmat'n No.: 2898

Filed: 20 March 2001

For: PEPTIDE ANTAGONISTS OF CGRP-RECEPTOR SUPERFAMILY AND  
METHODS OF USE

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**Remarks**

The Office Action mailed 26 September 2002 has been received and reviewed. Claims 29, 32, 33, 45, 46, 48, 50, 51 and 53 having been amended and claims 54 and 55 having been added, the pending claims are 21-26 and 29-55. Claims 34, 35, and 48-53 are currently withdrawn from examination, as drawn to non-elected inventions. Reconsideration and withdrawal of the rejections are respectfully requested.

Support for new claims 54 and 55 is found, for example, on p. 8, lines 6-15 and 18-20 of the specification. Support for the claim amendments is found throughout the specification. For example, support for the recitation "a CGRP-binding peptide" in amended claims 29, 48 and 51 is found on p. 8, line 16 of the specification; support for the recitation "in an amount effective to inhibit CGRP binding to one or more CGRP receptors" in amended claim 29 is found on p. 16, lines 4-6 of the specification; and support for amended claim 46 is found in original claim 46.

**AFFIRMATION OF ELECTION**

The Examiner has acknowledged the Applicant's election, with traverse, of Group I, claims 21-26 and 29-47. Applicant's again respectfully request reconsideration and withdrawal or modification of the restriction requirement. It is respectfully submitted that the inventions as claimed can be readily evaluated in one search without placing undue burden on the Examiner. And, were restriction to be effected between the claims of Groups I-III, a separate examination of the claims in these three groups would require substantial duplication of work on the part of the U.S. Patent and Trademark Office.

The Examiner has also acknowledged the Applicant's species election with traverse of SEQ ID NO:2. This election is made with traverse to the extent that it is understood that (a) the requirement will be withdrawn upon the finding of an allowable genus; and (b) any

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species withdrawn from consideration will be transferred to the elected subject matter unless it is found patentably distinct from the elected or allowed claims.

**Information Disclosure Statements**

A copy of the PTO-1449 mailed March 20, 2001, considered and initialed by the Examiner was received with the Office Action mailed September 26, 2002. It is noted that Ling et al., "Synthesis of Antigenic Determinant Tyr-CGRP=(27-37) of Calcitonin Gene-Related Peptide," *Chemical Abstracts*, 122(15):1117, Abstract No. 122:188122f (1995), has been lined through on the PTO-1449 and has not been considered by the Examiner. The Examiner has provided no explanation.

A copy of page 3 of the PTO-1449, previously mailed on March 20, 2001, citing Ling et al. and a copy of the Ling et al. abstract are provided as Exhibit A with this Response for consideration by the Examiner. If the Examiner cannot consider this reference, he is invited to explain why he is unable to do so.

**The Claim Objections**

The Examiner objected to claim 31 for encompassing a non-elected species, SEQ ID NO:1, and required the Applicant to amend the claims to recite upon only the elected invention. SEQ ID NO:1 is a non-elected species, which will be examined when a generic claim is indicated to be allowable. Applicants request this objection to claim 31 be held in abeyance, as the election of species requirement will be withdrawn upon the finding of an allowable genus.

**The 35 U.S.C. §112, Second Paragraph, Rejection**

The Examiner rejected claims 21-26, 29-33, and 36-47 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

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The Examiner rejected claim 29 as indefinite, as it is unclear what effect is achieved by the "contacting step." Claim 29 is drawn to a method for inhibiting CGRP binding to one or more CGRP receptors comprising contacting a CGRP receptor with a composition "in an amount effective to inhibit CGRP binding to one or more CGRP receptors." Thus, Applicant submits that the effect to be achieved by the contacting step is clear.

The Examiner rejected claims 32 and 33, asserting that there is insufficient antecedent basis in claim 29 for the recitation "Z is an antagonist." This objection is respectfully traversed. Claim 29 recites "wherein Z is a CGRP receptor-binding peptide." Dependent claims 32 and 33 are drawn to the method of claim 29, "wherein Z is an antagonist." Applicant's respectfully submit that adequate antecedent basis for this recitation is found in claim 29.

The Examiner rejected claim 45, asserting that there is insufficient antecedent basis in claim 43 for the recitation "R1 is." Claim 45 has been amended to depend from claim 37. Applicants respectfully submit that adequate antecedent basis for the recitation "R1" is found in claim 37.

The Examiner rejected claim 46 as indefinite in the recitation "a CGRP antagonist and a peptide or polypeptide having at least 15." As recommended by the Examiner, claim 46 has been amended to recite "the peptide is a CGRP antagonist having at least 15."

These amendments have been made to clarify the claims and do not further limit the claims. Withdrawal of the rejection of claims 21-26, 29-33, and 36-47 under 35 U.S.C. §112, second paragraph, is respectfully requested.

**The 35 U.S.C. §112, First Paragraph, Rejection**

Claims 21-26, 29-33, and 36-47 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

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Specifically, the Examiner asserted that the specification provides inadequate guidance for the preparation of peptide Z of the claimed method. Applicants respectfully disagree. Claim 29 and dependent claims 21-26 and 30-47 are drawn to methods of inhibiting CGRP binding to CGRP receptors by contacting a CGRP receptor with a composition comprising a peptide having the general formula  $R^1-X-Z$ , in an amount effective to inhibit CGRP binding to the CGRP receptor. Z is a CGRP receptor-binding peptide. Applicants respectfully submit that the specification provides adequate guidance for the preparation and use of such CGRP receptor-binding peptides. See, for example, p. 16, lines 13-22 and Example 2 of the specification.

Further, the Examiner asserted that the specification provides inadequate guidance for the preparation and use of the antagonistic peptides of claims 32 and 33. Applicants respectfully disagree. The peptides of dependent claims 32 and 33 are CGRP receptor-binding peptides that are antagonistic of human CGRP (claim 32) or  $\alpha$ -CGRP or  $\beta$ -CGRP (claim 33). Applicants submit that the specification provides adequate guidance for the preparation and use of the such antagonistic peptides. See, for example, p. 15, lines 19-25 and Examples 2 and 3. Thus, it would not require undue experimentation of one of skill in the art to make and use the antagonistic peptides of claims 32 and 33.

With this rejection under 35 U.S.C. 112, first paragraph, the Examiner asserted that "an antagonist of CGRP can be neither a vasoconstrictor nor a vasodilator, therefore, it must not be a vasoactive peptide." Applicant respectfully disagrees. While the specification states that the "term 'vasoactive peptide' refers to peptides that are capable of causing vasoconstriction or vasodilation," (p. 8, lines 14), the vasoactive peptides of the claimed invention are not limited to only peptides that cause vasoconstriction or vasodilation. As defined in the specification, the "term 'vasoactive peptide' as used herein refers to peptides with physiological activity, particularly, but not necessarily solely, directed in activity to the vascular system and preferably peptides with CGRP antagonist activity" (p. 11, lines 1-4 of the specification). Peptides with CGRP antagonist activity are peptides that inhibit CGRP activity (p. 15, lines 20-21). Thus, peptides with antagonist activity, that inhibit CGRP activity, qualify as vasoactive peptides, as

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defined by Applicant. And, as noted in the specification, a variety of vasoactive peptides that function as CGRP antagonists are known in the art (p.8, lines 18-20). Thus, it is respectfully submitted that an antagonist peptide is a vasoactive peptide.

For the reasons discussed above, Applicants request that the rejection of claims 21-26, 29-33, and 36-47 under 35 U.S.C. 112, first paragraph, be withdrawn.

**Summary**

It is respectfully submitted that the pending claims 21-26 and 29-53 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

**CERTIFICATE UNDER 37 CFR §1.8:**

The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on this 26<sup>th</sup> day of December, 2002, at 10:00 am (Central Time).

By: Kelly J. McNulty  
Printed Name: Kelly J. McNulty

Respectfully submitted for  
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APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS  
INCLUDING NOTATIONS TO INDICATE CHANGES MADE

Serial No.: 09/813,345

Docket No.: 180.0002 0102

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been shaded.

In the Title

The title has been amended as follows:

METHODS FOR INHIBITING CGRP BINDING

PEPTIDE ANTAGONISTS OF CGRP RECEPTOR SUPERFAMILY AND  
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In the Claims

For convenience, all pending claims are shown below.

21. The method of Claim 29 wherein the CGRP receptor is on a cell.
22. The method of Claim 29 wherein the CGRP receptor is cell free.
23. The method of Claim 21 wherein the cell is in culture.
24. The method of Claim 21 wherein the cell is part of a tissue.
25. The method of Claim 21 wherein the cell is in an animal.
26. The method of Claim 25 wherein the animal is a human.
29. (AMENDED) A method for inhibiting CGRP binding to one or more CGRP receptors comprising contacting a CGRP receptor with an effective amount of a composition comprising a peptide having the general formula:



wherein Z is a vasoactive CGRP receptor-binding peptide, R<sup>1</sup> is an organic group, X

is

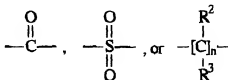
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and wherein  $\text{R}^2$  and  $\text{R}^3$  are independently H or an organic group and  $n$  is a whole integer between 1 and 10.

~~1. The method of Claim 29 wherein Z is a peptide fragment of at least 15 amino acids from CGRP.~~

30. The method of Claim 29 wherein Z is a peptide fragment of at least 15 amino acids from CGRP.

31. The method of Claim 30 wherein Z comprises the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2.

32. (AMENDED) The method of Claim 29 ~~30~~ wherein Z is an antagonist of human CGRP.

33. (AMENDED) The method of Claim 29 ~~30~~ wherein Z is an antagonist of  $\alpha$ -CGRP or  $\beta$ -CGRP.

34. The method of Claim 33 wherein Z comprises the amino acid sequence of SEQ ID NOS:6-17 and 23.

35. The method of Claim 33 wherein Z comprises the amino acid sequence of SEQ ID NOS:18-22.

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36. The method of claim 29 wherein Z is a CGRP antagonist peptide fragment selected from the group consisting of amylin, CGRP and adrenomedullin.
37. The method of Claim 29 wherein R<sup>1</sup> is an aromatic group, a heterocyclic group or an alkyl group and R<sup>2</sup> and R<sup>3</sup> are independently H, an aromatic group or an alkyl group.
38. The method of Claim 37 wherein R<sup>1</sup> is a C1-C4 alkyl group.
39. The method of Claim 38 wherein R<sup>1</sup> is a fluoroalkyl.
40. The method of Claim 38 wherein R<sup>2</sup> and R<sup>3</sup> are independently H, a C1-C4 alkyl group or a phenyl moiety.
41. The method of Claim 38 wherein R<sup>1</sup> is a C5-C10 aromatic group, a C5-C9 heterocyclic group or a C1-C4 alkyl group.
42. The method of Claim 41 wherein R<sup>2</sup> and R<sup>3</sup> are independently H or a C5-C10 aromatic group or a C1-C4 alkyl group.



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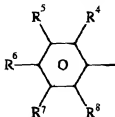
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43. The method of Claim 37 wherein  $R^1$  has the general formula:



- and wherein  $R^4$ - $R^8$  are each independently selected from the group of H, fluoro, chloro, bromo, iodo, nitro, nitrile (cyano), amino, N-methyl amino, N,N-dimethyl amino, hydroxy, methoxy, thiomethoxy (S-methyl), methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, trifluoromethyl, trifluoromethoxy, vinyl, acetamido, phenyl, toluyl, and methoxyphenyl.

44. The method of Claim 43 wherein  $R^6$  is trifluoromethyl and  $R^4$ ,  $R^5$ ,  $R^7$  and  $R^8$  are F.

45. (AMENDED) The method of Claim 43 wherein  $R^1$  is



and wherein Y is selected from the group consisting of O, NH, and S.

46. (AMENDED) The method of Claim 43 wherein the peptide is a CGRP antagonist having ~~and a peptide or peptide on~~ at least 15 consecutive amino acids selected from a protein from the group consisting of N- $\alpha$ -benzoyl- $\alpha$ -CGRP, N- $\alpha$ -benzyl- $\beta$ -CGRP, N- $\alpha$ -benzoyl- $\beta$ -CGRP and N- $\alpha$ -benzyl- $\alpha$ -CGRP, dibenzyl-h- $\alpha$ -CGRP and dibenzyl-h- $\beta$ -CGRP.

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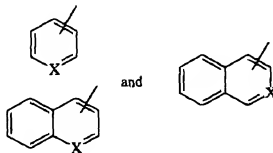
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47. The method of Claim 37 wherein  $R^1$  is selected from the group consisting

of:

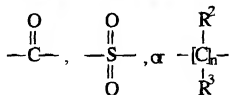


and wherein X is selected from the group consisting of C and N.

- 5 48. (AMENDED) An assay for identifying CGRP antagonists comprising:  
combining a peptide having the general formula:



wherein Z is a ~~vasoactive~~ ~~CGRP receptor binding~~ peptide,  $R^1$  is an organic group, X is



- 10 and wherein  $R^2$  and  $R^3$  are independently H or an organic group and n is a whole integer between  
1 and 10, with at least one CGRP receptor and a test CGRP antagonist with at least one CGRP  
receptor; and

comparing binding of the peptide to the CGRP receptor with binding of the test  
antagonist to the CGRP receptor, wherein improved binding of the test antagonist to the CGRP

- 15 receptor in the presence of the peptide identifies a candidate CGRP antagonist.

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49. The assay of claim 48 wherein Z is a peptide fragment of at least 15 amino acids from CGRP.

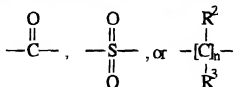
50. (AMENDED) The assay of claim 49 wherein Z is an antagonist of human CGRP.

51. (AMENDED) A method for identifying a CGRP receptor in a cell sample comprising: contacting a peptide having the general formula:

10



wherein Z is a ~~lysine~~ ~~CGRP-receptor-binding~~ peptide, R<sup>1</sup> is an organic group, X is



and wherein R<sup>2</sup> and R<sup>3</sup> are independently H or an organic group and n is a whole integer between 1 and 10, with a cell sample to detect binding of the peptide to the cell; and

15 isolating one or more receptors binding the peptide to the cell.

52. The assay of claim 51 wherein Z is a peptide fragment of at least 15 amino acids from CGRP.

53. (AMENDED) The assay of claim 51 wherein Z is an antagonist of human CGRP.

~~54. The method of claim 53 wherein Z is a lysine~~

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**55: (NEW) The method of claim 54 wherein the antagonist of human CGRP is**

<b>INFORMATION DISCLOSURE STATEMENT</b>	Atty. Docket No.: 180.0002 0102	Serial No.: unknown; (parent: 09/070,504)
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	Applicant(s): Derek D. SMITH et al.	
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df	Franc-Cereceda et al., "Calcitonin gene-related peptide but not substance P mimics capsaicin-induced coronary vasodilation in the pig", <i>Eur. J. Pharmacol.</i> 142: 235-243, 1987.
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	Kitamura et al., "Adrenomedullin: A Novel Hypotensive Peptide Isolated from Human Pheochromocytoma", <i>Biochemical and Biophysical Research Communications</i> , 192:553-560 1993.
	Leffert, J.D. et al., "Rat amylin: Cloning and tissue-specific expression in pancreatic islets", <i>Proc. Natl. Acad. Sci. USA</i> 86:3127-3130, 1989.
✓	Ling et al., "Synthesis of Antigenic Determinant Tyr-CGRP=(27-37) of Calcitonin Gene-Related Peptide," <i>Chinese Journal of Medicinal Chemistry</i> , 4(2):131-136 (1994).
	Ling et al., "Synthesis of Antigenic Determinant Tyr-CGRP=(27-37) of Calcitonin Gene-Related Peptide," <i>Chemical Abstracts</i> , 122(15):1117, Abstract No. 122:188122f (1995).
dy	Partial English-language translation of Ling et al., "Synthesis of Antigenic Determinant Tyr-CGRP=(27-37) of Calcitonin Gene-Related Peptide," <i>Chinese Journal of Medicinal Chemistry</i> , 4(2):131-136 (1994).

<b>EXAMINER</b> Dong Liang	<b>Date Considered</b> 9/16/02
*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

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